ANDA 73-099 5 mg (base)
73-101 25 mg (base)

MAR 28 1997

Pharmachemie USA, Inc.
Attention: Hellen de Kloet
U.S. Agent for Pharmachemie B.V.
323 Davis Street
Northborough, MA 01532

Dear Madam:

This is in reference to your abbreviated new drug applications dated January 13, 1989, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Leucovorin Calcium Tablets, USP.

Reference is also made to your correspondence dated March 20, 1996 and your amendments dated July 26, October 28, November 29, and December 16, 1996, and March 14, 1997.

We have completed the review of these abbreviated applications and have concluded that the drugs are safe and effective for use as recommended in the submitted labeling. Accordingly, the applications are approved. The Division of Bioequivalence has determined your Leucovorin Calcium Tablets, 5 mg and 25 mg, to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Wellcovorin® Tablets, 5 mg and 25 mg (base) respectively, of Glaxo Wellcome, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in these abbreviated applications require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for these abbreviated applications are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 73-099 and 73-101
Division File
Field Copy
HFD-600/Reading File
HFD-[redacted] 93
HFD-8/P.Savino
HFD-610/J.Phillips

Endorsements:

HFD-625/K.Furnkranz/11-13-96
HFD-613/C.Holquist/11-18-96
HFD-625/M.Smela/11-14-96
HFD-613/J.Grace/11-19-96
HFD-617/S.O'Keefe/11-27-96
x:\new\firmsnz\pharmach\ltrs&rev\73099app.pkg
F/T by: bc/12-2-96

APPROVE

may occur while neurological manifestations continue to progress.

WARNINGS

In the treatment of accidental overdosage of folic acid antagonists, leucovorin should be administered as promptly as possible. As the time interval between antifolate administration (e.g., methotrexate and leucovorin rescue increases, leucovorin's effectiveness in counteracting hematologic toxicity decreases.

Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

Delayed methotrexate excretion may be caused by a third space fluid accumulation (i.e. ascites, pleural effusion), renal insufficiency, or inadequate hydration. Under such circumstances, higher doses of leucovorin or prolonged administration may be indicated. Doses higher than those recommended for oral use must be given intravenously.

Leucovorin may enhance the toxicity of fluorouracil. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil. Concomitant granulocytopenia and fever were present in some but not all of the patients.

The concomitant use of leucovorin with trimethoprim-sulfamethoxazole for the acute treatment of *Pneumocystis carinii* pneumonia in patients with HIV infection was associated with increased rates of treatment failure and morbidity in a placebo-controlled study.

PRECAUTIONS

General: Parenteral administration of leucovorin is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb the leucovorin. Leucovorin has no effect on other established toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

Drug interactions: Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children.

Preliminary animal and human studies have shown that small quantities of systemically administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Leucovorin may enhance the toxicity of fluorouracil (see WARNINGS).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Animal reproduction studies have not been conducted with leucovorin. It is also not known whether leucovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Leucovorin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when leucovorin is administered to a nursing mother.

Pediatric Use: See "Drug Interactions" subsection.

ADVERSE REACTIONS

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following the administration of both oral and parenteral leucovorin.

OVERDOSAGE

Excessive amounts of leucovorin may nullify the chemotherapeutic effect of folic acid antagonists.

DOSAGE AND ADMINISTRATION

Leucovorin Calcium Tablets are intended for oral administration. Because absorption is saturable, oral administration of doses greater than 25 mg is not recommended.

Impaired Methotrexate Elimination or Inadvertent Overdosage: Leucovorin rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is delayed excretion (see WARNINGS). Leucovorin 15 mg (10 mg/m^2) should be administered IM, IV, or PO every 6 hours until the serum methotrexate level is less than 10^{-8}M. In the presence of gastrointestinal toxicity, nausea or vomiting, leucovorin should be administered parenterally.

Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If the 24 hour serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than 5×10^{-8}M or the 48 hour level is greater than 9×10^{-7}M, the dose of leucovorin should be increased to 150 mg (100 mg/m^2) IV every 3 hours until the methotrexate level is less than 10^{-8}M. Doses greater than 25 mg should be given parenterally (see CLINICAL PHARMACOLOGY).

Hydration (3L/d) and urinary alkalinization with sodium bicarbonate should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

The recommended dose of leucovorin to counteract hematologic toxicity from folic acid antagonists with less affinity for mammalian dihydrofolate reductase than methotrexate (i.e. trimethoprim, pyrimethamine) is substantially less and 5 to 15 mg of leucovorin per day has been recommended by some investigators.

Patients who experience delayed early methotrexate elimination are likely to develop reversible non-oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration, which are significant but less severe. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g., medications which may interfere with methotrexate elimination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

HOW SUPPLIED

Leucovorin Calcium Tablets equivalent to 5 mg of leucovorin are round, yellowish-white, scored tablets, identified with PCH on one side and RES above the score and 5 below the score on the other side, available in packages of 50 tablets (10 strips of 5 tablets), NDC 53989-1601-78, and in containers with respectively 30 or 100 tablets, NDC 53989-1601-30 or NDC 53989-1601-05.

Leucovorin Calcium Tablets equivalent to 25 mg of leucovorin are round, yellowish-white, scored tablets, identified with PCH on one side and RES above the score and 25 below the score on the other side, available in packages of 10 tablets (2 strips of 5 tablets), NDC 53989-1603-78, and in containers with respectively 25 or 100 tablets, NDC 53989-1603-25 or NDC 53989-1603-05.

Store between 15° to 25°C (59° to 77°F) [see USP].

REFERENCES

1. Grem JL, Shoemaker DD, Petrelli NJ, Douglass HO Jr. Severe and fatal toxic effects observed in treatment with high- and low-dose leucovorin plus 5-fluorouracil for colorectal carcinoma. *Cancer Treat Rep* 1987; 71: 1122.

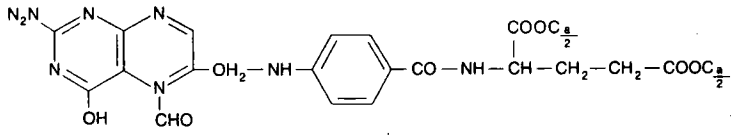
2. Link MP, Goorin AM, Miser AW, et al. The effect of adjuvant chemotherapy on relapse-free survival patients with osteosarcoma of the extremity. *N Engl J Med* 1986; 314: 1600-1606.

LEUCOVORIN CALCIUM TABLETS USP 5 MG AND 25 MG

DESCRIPTION

Leucovorin Calcium Tablets contain either 5 mg or 25 mg of leucovorin as the calcium salt of *N*-[4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)-methyl]amino]benzoyl]-L-glutamic acid. This is equivalent to 5.40 mg or 27.01 mg of anhydrous leucovorin calcium.

Leucovorin is a water soluble form of reduced folate in the folate group; it is useful as an antidote to drugs which act as folic acid antagonists. These tablets are intended for oral administration only. The structural formula of leucovorin calcium (which normally exists as a hydrate, 8% to 15% water) is:



$C_{20}H_{21}CaN_7O_7$ 511.51

Each tablet for oral administration contains leucovorin calcium, equivalent to 5 mg or 25 mg of leucovorin. The inactive ingredients are lactose monohydrate, potato starch, povidone, magnesium stearate and colloidal silicon dioxide.

CLINICAL PHARMACOLOGY

Leucovorin is a racemic mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid. The biologically active component of the mixture is the (-)-*L*-isomer, known as *Citrovorum factor*, or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. Following oral administration, leucovorin is rapidly absorbed and enters the general body pool of *reduced folates*. The increase in plasma and serum folate activity (determined microbiologically with *Lactobacillus casei*) seen after oral administration of leucovorin is predominantly due to 5-methyltetrahydrofolate.

Twenty normal men were given a single, oral 5 mg dose (7.5 mg/m²) of leucovorin calcium and serum folate concentrations were assayed with *L casei*. Mean values observed (± one standard error) were:

a) Time to peak serum folate concentration: 1.72 ± 0.08 hrs.,
b) Peak serum folate concentration achieved: 268 ± 18 ng/mL,
c) Serum folate half-disappearance time: 3.5 hours.

Oral tablets yielded areas under the serum folate concentration-time curves (AUC's) that were 12% greater than equal amounts of leucovorin given intramuscularly and equal to the same amounts given intravenously.

Oral absorption of leucovorin is saturable at doses above 25 mg. The apparent bioavailability of leucovorin was 97% for 25 mg, 75% for 50 mg and 37% for 100 mg.

INDICATIONS AND USAGE

Leucovorin Calcium Tablets are indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists.

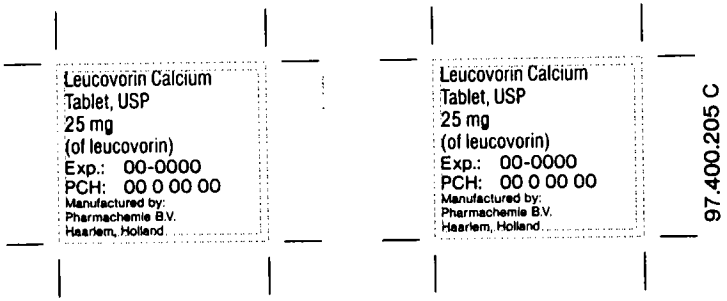
CONTRAINDICATIONS

Leucovorin is improper therapy for pernicious anemia and other megaloblastic anemias secondary to the lack of vitamin B_{12}. A hematologic remission

PHARMACHEMIE B.V.
P.O. Box 552
OPG Groep 2003 RN Haarlem, The Netherlands 0297.9v.WvO

PHARMACHEMIE B.V. - HAARLEM/ZAANDAM				
DATUM BINNENKOMST:	Q.A	V.V.	Q.C.	IN

BASISTEKST	97.400.205 C
VERSIE	C
VERPAKKING	EAV



PHARMACHEMIE B.V. - HAARLEM/ZAANDAM				
DATUM BINNENKOMST:	Q.A	V.V.	Q.C.	IN

BASISTEKST	97.400.205 C
VERSIE	C
VERPAKKING	EAV

Leucovorin Calcium
Tablet, USP
25 mg
(of leucovorin)
Exp.: 00-0000
PCH: 00 0 00 00
Manufactured by:
Pharmachemie B.V.
Haarlem, Holland

Leucovorin Calcium
Tablet, USP
25 mg
(of leucovorin)
Exp.: 00-0000
PCH: 00 0 00 00
Manufactured by:
Pharmachemie B.V.
Haarlem, Holland

97.400.205 C

PHARMACHEMIE B.V. - HAARLEM/ZAANDAM				
DATUM BINNENKOMST:	Q.A	V.V.	Q.C.	IN

BASISTEKST	97.400.205 C
VERSIE	C
VERPAKKING	EAV

Leucovorin Calcium
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Haarlem, Holland

Leucovorin Calcium
Tablet, USP
25 mg
(of leucovorin)
Exp.: 00-0000
PCH: 00 0 00 00
Manufactured by:
Pharmachemie B.V.
Haarlem, Holland

97.400.205 C

ANDA #73-099 & 73-101
Addendum to Chemistry Review #5
Leucovorin Tablets USP, 5 and 25 mg.

The latest EER was issued 2/23/96 for the listed firms. The EER was completed and apparently considered generally acceptable on October 10, 1996. A copy of the EER, is not found in the ANDAs. However, there were several open issues resulting from the inspection that need evaluation by the review chemist as a result of deficiencies in the laboratory practices of the firm over the years. These deficiencies were felt to potentially impact on the laboratory results submitted in the ANDA and should be evaluated by the chemistry reviewer. Refer to the attached 10/9/96 memorandum from HFD-322. These issues have been evaluated below:

A. Firm has had problems with the USP calibrators for their dissolution apparati in their R&D and QC labs. The firm had numerous calibrator failures yet they never followed with an investigation of the reason for the failures. The Leucovorin Calcium Tablets dissolution profiles and innovator comparisons were performed at that time.
Evaluation: In 1987, firm tested the operation of their dissolution apparatus under 4 conditions using the 2 calibrator tablets. 2 of the 48 calibrators failed. Although this may result in the failure of the calibration test, it would not have materially affected the results of the products tested at that time. Pharmachemie has performed yearly validation since that time and has not had any problems. Satisfactory.

B. The firm had a lack of data to show that their Leucovorin assay method was comparable to the USP method.

Evaluation: Pharmachemie performed a comparative analysis of the 2 methods and an acceptable mean difference (0.7%) was found. Firm has subsequently adopted the USP method. Satisfactory.

C. An analysis of a research batch (not associated with the ANDA application) was not performed as per the firm's method. The concentration of the sample solutions was not within the range of concentrations at which the method was validated.

Evaluation: Pharmachemie indicated that the assay method was the USP method. Satisfactory.

D. Firm's test failed to include system suitability criteria.

Evaluation: Pharmachemie has added systems suitability

criteria to their cest method.

E. There was no data to demonstrate lack of interference of the excipients/degradants on the drug product assay.

Evaluation: The firm has subsequently submitted the appropriate information demonstrating lack of placebo interference for the Leucovorin Calcium drug product. Satisfactory.

F. Firm utilized a content uniformity method that was different from the assay method, and failed to determine the correction factors as indicated in the USP for content uniformity testing.

Evaluation: The firm stated that the comparison was performed as per the USP and, based on the data, no correction factors were necessary. Pharmachemie reported data demonstrates that a correction factor was not needed for the Leucovorin Calcium tablets method. Satisfactory.

G. The Firm determines the levels of impurities or degradants in the drug product at the same sensitivity as for the assay. The investigators recommended that the impurities/degradants be evaluated at higher sensitivity.

Evaluation: Pharmachemie indicated that impurities are determined as a percentage of the and that it is imperative that be integrated accurately in The firm submitted a sample to demonstrate. The firm has also committed to include of standard solution at a desired limit level to demonstrate that the system could adequately integrate t that level. Satisfactory.

H. The Firm calculated the percent of impurities in the drug product were calculated incorrectly.

Evaluation: The firm revised the method of calculation of known impurities as a result of the update of the ANDA. Total impurities is now calculated properly. Satisfactory.

CONCLUSION: The issues indicated by the field investigator should not have significant impact on the drug product manufactured at the site at the time the spurious results were reported to support the ANDA. From a CMC standpoint, the ANDA is approvable. The most troubling issues (dissolution calibration failures since 1992) would probably not have significant impact on the actual dissolution

results reported for the drug product.

Kenneth J. Furnkranz
Senior Review Scientist, HFD-625

11/14/96

Michael Smela Jr.
Supervisory Chemist, HFD-625

cc: ANDA 73-099; ANDA 73-101 (Orig)
ANDA 73-099; ANDA 73-101 (Dup)
Division File
Field Copy

11/13/96

Endorsements:
HFD-625/K.Furnkran
HFD-625/M.Smela
X:\new\firmsnz\pharmach\ltrs&rev\73-099app.pkg
F/T by:
Approve

1. CHEMIST'S REVIEW NO. 5

2. ANDA 73-099 (5 mg)
73-101 (25 mg)

3. NAME AND ADDRESS OF APPLICANT
Pharmachemie USA, Inc.
US Agent for Pharmachemic B.V.
P.O. Box 145
Oradell, NJ 07649

4. LEGAL BASIS FOR ANDA SUBMISSION
Wellcovorin Tablets (Burroughs Welcome)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Leucovorin Calcium Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

APPLICANT:
Original Filing - 1/13/89
A copy of a 9/5/88 letter from the firm to Dr. Charles Ise regarding bio issues (batch sizes) is also included.
Letter re: Bio Issues - 4/11/89
O-NC (Bio material) - 4/18/89
ANDA Amend - 7/19/90 - Response to N/A letter #1
ANDA Amend - 10/12/94 - Response to N/A letter #2
ANDA Amend - 2/14/96 - Response to N/A letter #3
* O-NC - 3/20/96
* ANDA Amend - 7/26/96 - Response to N/A letter #4

FDA:
Acknowledgement: 2/2/89
A copy of a 10/21/88 letter from Dr. Ise to firm granting a batch size waiver is also present.
Bio study approval letter: 4/17/89
Review of additional bio material: 5/25/89
N/A (chem/label def) letter/review # 1: 9/8/89
N/A letter/review #2 - 1/14/91
N/A letter/review #3 - 3/16/95
N/A letter/review #4 - 4/12/96

OTHER:
EER issued 3/7/95 found unacceptable on 7/31/95. Firms were not ready for inspection.
EER Resubmitted on 2/23/96. Awaiting final report.

10. PHARMACOLOGICAL CATEGORY
Counteract folic acid antagonists

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablet

14. POTENCY
73-099 (5 mg)
73-101 (25 mg)

15. CHEMICAL NAME AND STRUCTURE
Leucovorin Calcium USP

16. RECORDS AND REPORTS- None

17. COMMENTS
a. Awaiting satisfactory EER and resolution of labeling.

18. CONCLUSIONS AND RECOMMENDATIONS
CHEMISTRY CLOSED. Pending EER and labeling issues.

19. REVIEWER:
Kenneth J. Furnkranz

DATE COMPLETED:
August 14, 1996

cc: ANDA #73-099, 73-101
ANDA #73-099, 73-101/DUP/Duplicate Jackets (2)
HFD-600/Reading file
Field Copy

8/14/96

Endorsements:
HFD-625/K.Furnkranz
HFD-625/M.Smela
F/T by
x:\new\firmsnz\pharmach\ltrs&rev\73099a05.fkf
APPROVE

8/15/96

ANDA 73-101

Pharmachemie U.S.A., Inc.
Attention: Mr. J. David Hayden
P.O. Box 145
Oradell, NJ 07649

Dear Sir:

Reference is made to the bioavailability study and dissolution data you submitted on January 13, 1989 for Leucovorin Calcium Tablets , 25 mg.

The study and dissolution data have been reviewed by our Division Bioequivalence and they have the following comments:

"1. The bioequivalence study conducted by Pharmachemie USA on its Leucovorin Calcium Tablets, 25 mg, lot # 870729, comparing it to Wellcovorin Tablets, 25 mg, manufactured by Burroughs Wellcome, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Pharmachemie USA's Leucovorin Calcium Tablets, 25 mg tablet, is bioequivalent to the reference product, Wellcovorin Tablets, 25 mg, manufactured by Burroughs Wellcome.

2. The dissolution testing conducted by Pharmachemie USA on its Leucovorin Calcium Tablets, 25 mg, lot 870729, is acceptable.

3. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is acceptable.

4. The dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of Leucovorin Calcium in the tablet is dissolved in 45 minutes."

A decision regarding the approvability of an application is not final until the approval letter for that application is issued. Accordingly, any bioequivalence determination communicated in this letter is preliminary. The bioequivalence determination may be revised after a supervisory review of the entire application, upon consideration of the chemistry, manufacturing and controls, labeling, or other scientific or regulatory issues. A revised determination may necessitate an additional study(ies), or may conclude that the proposed formulation is not approvable.

Sincerely yours,

DRosen 4/17/89

Martin Seife 4/17/89

Martin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards

cc:
HFD-232
DRosen/DShostak
kl/4-14-89/2300b
bio letters

Leucovorin Calcium Tablets
25 mg Tablet
ANDA # 73-101
Reviewer: Moo K. Park
Wang # 5414f

Pharmachemie USA
Oradell, NJ
Submission Date:
January 13, 1989

4 6 9

Review of a Bioequivalence Study and Dissolution Data

I. Objective

To review the firm's bioequivalence study and dissolution data comparing its Leucovorin Calcium tablets, 25 mg, to Burroughs Wellcome's Wellcovorin, 25 mg tablet.

II. Background

Leucovorin, also known as folinic acid, is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid, the active form of folic acid, which is involved as a cofactor in the biosynthesis of purines and pyrimidines. Leucovorin is used principally as an antidote to folic acid antagonists, such as methotrexate, which block the conversion of folic acid to tetrahydrofolate by binding the enzyme dihydrofolate reductase.

After oral administration, leucovorin is rapidly absorbed and converted into 5- methyltetrahydrofolate (5-MeTHF). Peak plasma concentrations of 5-MeTHF are usually reached within 2 hours. The distribution half-life of 5-MeTHF is about 2-3 hours and the terminal half-life is about 10-13 hours.

Serum protein binding of 5-MeTHF is about 60-70%.

Available dosage forms are oral tablets, oral solutions , and injectable solutions.

For oral tablets, 5 mg, 10 mg, 15 mg, and 25 mg tablets are available.

III. Study Details

1. Protocol #: PBR-870119-2

2. Study site:

3. Sponsor: Pharmachemie B.V.
Haarlem, The Netherlands

4. Study Director:

5. Investigators:

6. Study dates: September 22 - October 11, 1987

7. Study design: Open, randomized, single dose, two-treatment, two-period, crossover.

8. Subjects: 24 healthy male subjects (20-40 years)

9. Treatments:

   (a) Test product: 1 x 25 mg Rescuvolin^{R} Tablets, 25 mg, manufactured by Pharmachemie B.V., lot # 870729

   (b) Reference product: 1 x 25 mg Wellcovorin, 25 mg tablet, manufactured by Burroughs Wellcome. lot # 6 J 3064

10. Washout period: Two weeks

11. Food and fluid intake: Overnight fasting for 10 hours prior to and 4 hours after the dosing with 240 ml of water.

12. Drug administration:

    1 x 25 mg tablet at 0 hour with 240 mL of water.

13. Blood sampling:

    Blood sample of 10 mL at each time point was collected and immediately cooled and centrifuged to separate the plasma. The plasma samples were stored at -20°C for future assay. Blood sampling was done at 0, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0, 30.0, 36.0, and 48.0 hours.

14. Subject control:

    Inclusion and exclusion criteria were established and followed. The subjects were housed in the Clinical Research Center from the evening preceding day of each study period until 24 hours after the dosing. During the period, the subjects were served with standard menus.

15. Statistical evaluation:

    The raw data for each concentration-time point and the parameters, C_{MAX}, $t_{1/2}$ and AUC of 5-methyl THF were analyzed for differences with multifactor ANOVA, using the computer program A model determining the effect of sequence, subject within sequence, period, and formulation was used for the ANOVA. Based on the results from ANOVA, 90% confidence intervals were calculated for the difference between parameters with different treatments. The parameter, t_{MAX}, was analyzed non-parametrically with Friedman two-way analysis, using the computer program

IV. Batch size and assay data

1. Batch size of the test product

lot # 870729:
A waiver of the requirement of a minimum batch size of 100,000 dosage unit was granted. (October 21, 1988)

2. Assay data

(a) Content uniformity of the test product

Batch #: 870729
Strength: 25 mg of leucovorin per tablet as the calcium salt
Number of tablets: 10
Assay:
Content uniformity: Mean 102.6%
S.D. 0.76%
C.V. 0.74 %

(b) Content uniformity of the reference product

Batch # 6 J3064
Strength: 25 mg of leucovorin per tablet as the calcium salt
Assay:
Content uniformity: Mean 107.0
S.D. 1.64%
C.V. 1.53%

V. Assay Method

VI. In Vivo Results with Statistical Analysis

1. 5-methyl THF Plasma Levels

Time, hr	Test Product Mean (SD)	Reference Product Mean (SD)	**Significance of the Difference
0	4 (3) ng/mL	3 (2) ng/mL	NS
0.25	11.2 (7.5)	13.9 (8.5)	S
0.50	59.7 (28.9)	68.3 (33.9)	NS
0.75	134 (54.0)	139 (55.6)	NS
1.0	202 (72.5)	200 (57.4)	NS
1.5	297 (72.0)	290 (57.4)	NS
2.0	329 (78.0)	332 (63.1)	NS
3.0	283 (72.2)	294 (67.3)	NS
4.0	206 (52.0)	207 (45.6)	NS
5.0	136 (37.1)	141 (32.3)	NS
6.0	92.9 (23.7)	96.0 (20.9)	NS
8.0	53.7 (12.1)	54.4 (15.0)	NS
10.0	39.7 (9.6)	38.1 (11.4)	NS
12.0	25.6 (7.0)	25.8 (8.1)	NS
16.0	14.5 (4)	14.4 (5)	NS
20.0	11.5 (4)	11.7 (3)	NS
24.0	11.9 (5)	9.9 (4)	S
30.0	7.2 (3)	6.1 (3)	S
36.0	6.7 (3)	5.4 (3)	S
48.0	6.3 (4)	5.2 (3)	NS

**95% Confidence

2. Pharmacokinetic Parameters

Parameter	Test Product Mean (SD)	Reference Product Mean (SD)	T/R	90% Confidence Interval
$AUC_{0-48\ hrs}$, ng.h/mL	1845.9 (357.8)	1834.3 (336.0)	1.006	93.1-108.1%
AUC_{0-inf}, ng.h/mL	1908.6 (371.7)	1878.4 (352.7)	0.914	94.2-109.0%
C_{MAX}, ng/mL	341.6 (69.7)	343.7 (50.3)	0.994	93.5-105.3%
t_{MAX}, h	2.05 (0.47)	2.17 (0.59)	--	--
$t_{1/2}$, h	3.90 (0.78)	3.75 (0.54)	--	--

VII. Dissolution Data

1. Formula comparison of test and reference products

Each tablet contains:

	Test Product	Reference Product
Leucovorin Calcium	27.01 mg	27.01 mg
Lactose		*
Potato Starch		
Povidine		*
Magnesium Stearate		*
Colloidal Silicon Dioxide		
Total	165	
Corn Starch		*
FD&C Yellow No. 6 Lake		*

*Quantity unknown

2. Dissolution testing

The firm used the FDA dissolution specifications:

NLT 45 minutes
900 mL water at 37°C
USP XXI Apparatus II (paddle), 50 rpm
Assayed by UV absorption at 287 nm.

The dissolution testing results are shown on Table I attached. The data are acceptable.

VIII. Comments

1. The 90% confidence intervals of test product/reference product ratios for $AUC_{0-48\ hrs}$, AUC_{0-inf}, and C_{MAX} were 93.1-108.1%, 94.2-109.0%, and 93.5-105.3%, respectively.

2. The plasma levels of 5-methyl THF at each sampling time for the test and reference products show no significant differences most of the time. Minor differences were observed at 0.25, 24, 30, and 36 hours.

3. Plasma levels of 5-methyl THF, a major metabolite, were measured by method. The assay method is acceptable based on precision and accuracy data.

4. The dissolution testing on the test and reference products is acceptable. The dissolution data satisfy the FDA dissolution specifications:

NLT 45 minutes
900 mL water at 37°C
USP XXI Apparatus II (paddle), 50 rpm
UV absorption at 287 nm

5. The batch size of the test product used in the bioequivalence study was tablets. The Agency granted the firm's request for a waiver of a minimum batch size requirement.

IX. Recommendations

1. The bioequivalence study conducted by Pharmachemie USA on its Leucovorin Calcium Tablets, 25 mg, lot # 870729, comparing it to Wellcovorin Tablets, 25 mg, manufactured by Burroughs Wellcome, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Pharmachemie USA's Leucovorin Calcium Tablets, 25 mg tablet, is bioequivalent to the reference product, Wellcoverin Tablets, 25 mg, manufactured by Burroughs Wellcome.

2. Therapeutic Equivalence Recommendation:

   The Division of Bioequivalence recommends that THE PRODUCT SHOULD BE CODED AB IN THE THERAPEUTIC EQUIVALENCE LIST.

3. The dissolution testing conducted by Pharmachemie USA on its Leucovorin Calcium Tablets, 25 mg, lot 870729, is acceptable.

4. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is approvable.

5. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of Leucovorin Calcium in the tablet is dissolved in 45 minutes.

The firm should be informed of the Recommendations.

Moo K. Park, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

MKPark/rlh/03-20-89/Wang #5414f

cc: ANDA # 73-101 original, HFD-230, HFD-200 (Hare), HFD-22 (Hooton), HFD-258 (Mhatre, Park), Drug File

Drug (Generic Name): Leucovorin Calcium Tablets 25 mg Firm: Pharmachemie US.

ANDA # 73-101 Submission Date: Jan 13, 1989

Table I- In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXI Basket ____ Paddle X RPM 50 No. Units Tested: 12

Medium: Water at 37°C Volume: 900 ml

Reference Drug; (Manuf.): Wellcovorin, 25mg, Burroughs Wellcome

Assay Methodology: _____

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) (Hr.)	Test Product Lot # 870729 Strength (mg) 25mg Mean % Dissolved	Range	(CV)	Reference Product Lot # GJ3064 Strength (mg) 25 Mean % Dissolved	Range	(CV)
15 min	57		(7.4)	98		(4.0)
30	93		(3.4)	105		(3.5)
45	102		(1.9)	105		(3.5)
60	102		(1.9)	105		(3.5)
			( )			( )

	Lot # ____ Strength (mg) ____			Lot # ____ Strength (mg) ____		
			( )			(
			( )			(
			( )			(
			( )			(
			( )			(

6/7/89

63

Leucovorin Calcium Tablets
25 mg Tablet
ANDA # 73-101
Reviewer: Moo K. Park
Wang # 5676f

5 25 89

Pharmachemie USA
Oradell, NJ
Submission Date:
April 18, 1989

Review of Additional Information

The firm submitted additional information on the assay validation of plasma samples and raw analytical data of five subjects upon request from the Division of Bioequivalence.

The submitted information fulfilled the requirements of the Division of Bioequivalence and are acceptable.

Moo K. Park, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

MKPark/rlh/05-19-89/Wang #5676f

cc: ANDA # 73-101 original, HFD-230, HFD-200 (Hare), HFD-22 (Hooton), HFD-258 (Mhatre, Park), Drug File